REMARKS

Status of the Claims

Claims 34-35, 37-40, 42-44, 46, 49-51, 54, and 56-61 are pending in the present application, Claims 1-33, 36, 41, 45, 47, 48, 52, and 53 having been previously canceled, Claim 55 having been canceled herein, and new Claims 56-61 having been added in the present amendment. Claims 34, 35, 40, 42, 43, 46, 50, 51, and 54 have been amended to address an indefiniteness rejection.

Summary of the Telephone Interview with the Examiner

On November 21, 2006, applicants' attorney (Michael C. King, Registration No. 44,832) contacted Examiner Gabel via telephone to discuss various issues identified in the Office Action dated August 28, 2006. Two supervising Examiners also participated in the discussion.

A first issue that was discussed was the Examiner's rejection of various claims as being indefinite, essentially because one probe having one optical signaling component satisfied a condition recited in step (a), but not step (b). Applicants' attorney suggested that this simply represented a narrowing limitation, as opposed to an indefiniteness issue. The Examiners collectively disagreed, and potentially acceptable language was discussed. No specific language was agreed upon; however, applicants' attorney believed that the issue had been defined well enough to enable applicants' attorney to draft acceptable language for amending the claim.

Another issue discussed was the rejection of the claims based on Garini (U.S. Patent No. 6,066,459). Applicants' attorney explained how the pending claims required the simultaneous generation of a plurality of spectrally distinguishable images, and further discussed the operating principles disclosed by Garini, who employs an adjustable interferometer to successively generate a plurality of spectrally distinguishable images. The significance of Garini's use of the term "*simultaneous*" was also discussed (this term was used to distinguish Garini's technique over that employed by slit-type interferometers, which generate an image by collecting a frame of data using a scanning function, whereas Garini collects data from all pixels ***in a single image*** simultaneously, but collects successive images sequentially). Applicants' attorney further discussed why Garini's technique required that there be no relative movement between the object and the imaging systems (because such motion would prevent the successive images from being properly synchronized). Based on this discussion and an analysis of the existing claim language, the Examiners collectively agreed that the pending claims distinguished over Garini due to the step of *simultaneously generating a plurality of images*.

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Applicants' attorney indicated that a further amendment addressing the indefiniteness rejection noted above would be submitted.

Applicants' attorney would like to thank Examiner Gabel and the Supervising Examiners for taking the time to discuss the issues noted above during the telephone interview, as this discussion was very helpful in substantially advancing the prosecution of the present application.

<u>Rejections of Claims 34, 35, and 37-40, 42-44, 46, 49-51, 54, and 55 under 35 U.S.C.§ 112</u>

The Examiner asserts that Claims 34, 35, and 37-40, 42-44, 46, 49-51, 54, and 55 are indefinite because of an inconsistency between step (a) and step (b), as exemplified in Claims 34 and 42 (the Examiner noting that a similar issue arises in other claims). The inconsistency is that step (a) recites *at least one optical signaling component*, and step (b) recites a plurality of different optical signaling components.

Having discussed this issue in the above noted telephone interview, applicants have amended independent Claims 34, 42, and 54 to replace the indefinite language, thereby obviating the rejection (Claim 55 having been canceled herein, thus rendering the rejection of Claim 55 moot). The amendments to Claims 35, 40, 43, 46, 50, and 51 were required to avoid any antecedent basis type issues introduced by the amendments to the independent claims.

In place of the indefinite language, independent Claims 34 and 54 have been amended to recite (in part):

(a) labeling the feature such that a plurality of different optical signaling components become bound to said feature, probes suitable for so labeling the feature comprising:

(i) a single type of probe comprising a binding element that selectively binds to at least a portion of the feature, and a plurality of optical signaling components, at least two of which are different, thereby enabling the plurality of different optical signaling components to be bound to said feature; and

(ii) two different types of probes, each of which comprises a binding element that selectively binds to at least a portion of the feature, and at least one optical signaling component, such that the optical signaling components of the two different types of probes are not identical, thereby enabling the plurality of different optical signaling components to be bound to said feature;

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This amendment is entirely consistent with the specification and the previously presented claims, and avoids the indefiniteness issue related to the use of a single probe with a single optical signaling component. Note that the language recited above is quite similar in result to the "capable of" language discussed by one of the Supervising Examiners in the above-noted telephone interview.

In place of the indefinite language, independent Claim 42 has been amended to recite:

(a) for each specific feature to be detected, providing at least one type of probe suitable for uniquely labeling the specific feature, types of probes suitable for so labeling each specific feature comprising:

(i) one type of probe comprising a binding element that selectively binds to at least a portion of said specific feature, and a plurality of optical signaling components, at least two of which are different, thereby enabling a plurality of different optical signaling components to be bound to said specific feature if said specific feature is part of the object; and

(ii) two different types of probes, each of which comprises a binding element that selectively binds to at least a portion of said specific feature, and at least one optical signaling component, one of the two different types of probes including a different optical signaling component than the other, thereby enabling a plurality of different optical signaling components to be bound to said specific feature if said specific feature is part of the object;

(b) exposing said object to each type of probe required to uniquely label each specific feature that is part of the object;

Having addressed the indefiniteness rejection of Claims 34, 35, and 37-40, 42-44, 46, 49-51, and 54 by amending the claims as described above, applicants respectfully request that the rejection be withdrawn.

<u>Rejection of Claims 34, 35, 37-40, 42-44, 46, 49-51 under 35 U.S.C. § 102</u>

The Examiner has rejected Claims 34, 35, 37-40, 42-44, 46, and 49-51 under 35 U.S.C. § 102 as being anticipated by Garini (U.S. Patent No. 6,066,459). The Examiner asserts that Garini discloses each element of applicants' claimed invention. Applicants respectfully disagree for the following reasons.

Independent Claims 34 and 42 are distinguishable over Garini because such claims recite the step of ***simultaneously*** generating a plurality of images. FIGURES 3, 14, 18, and 19 are exemplary of this aspect of the invention defined in Claims 34 and 42. As noted below, Garini's technique is

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based on acquiring a plurality of images successively over time (i.e., not simultaneously); thus, Garini does not teach or suggest dispersing light to ***simultaneously*** **generate a plurality of spectrally different images**.

The Examiner is correct that Garini's technique and applicants' technique can be used to analyze cellular features. The Examiner is further correct in noting that Garini discloses collecting a plurality of spectrally distinguishable images to enable cellular features to be analyzed, and that for each image collected, all pixels in the image are collected simultaneously. However, such a technique *is not* equivalent to the claimed technique of simultaneously generating a plurality of images.

To recognize this distinction, it is critically important to understand how Garini collects the spectral cube of data or spectral image that is analyzed to detect probes. Note that Garini specifically defines a *spectral image* as a ***sequence of images*** representing the intensity of the same two-dimensional plane (i.e., the sample) at different wavelengths (column 17, first full paragraph). Clearly, the plurality of images disclosed by Garini are collected sequentially. These images (which are collected sequentially over a single exposure period), are analogous to frames in a short video clip. Garini's Table 1 explicitly indicates that the exposure times (i.e., the length of the video clip) range from about 5-50 seconds, and are typically 25 seconds. During that exposure, a number of different images or frames are collected. These frames are collected as follows (see Garini's FIGURE 2, which represents a preferred imaging system more fully described in a different patent application; the Garini patent focusing on how to manipulate and use data collected using a system described in a different patent): Light from an object is directed to an interferometer. The interferometer separates light from the object into two different light paths. The two different light paths are recombined and directed onto a detector (i.e., a CCD or digital camera). An image or frame is formed on the detector. All of the data for each pixel in the image/frame are collected simultaneously. Significantly, the data in that single image/frame alone is not sufficient to carry out Garini's method. Additional frames must be collected as the settings of the interferometer are changed, to generate the spectral cube of data. The settings of the interferometer relate to how the optical path difference (OPD) in the interferometer changes between different frames (and these settings determine the wavelength difference between successive frames). Note that whenever the OPD in the interferometer is changed, the spectral properties of the image collected on the detector

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will change. Thus, if data are collected for five different OPDs, then five different frames or images are collected. Those five different frames are collected *sequentially* (i.e., over time, during a single continuous exposure, in the same manner that a video clip is generated).

Thus, once a first frame has been collected, the optical path difference (OPD) in the interferometer is changed, ***and a new frame is subsequently collected***. The significance Garini places on the simultaneous collection of data from all pixels ***in a frame*** is because some prior art techniques (slit type interferometers) would generate a single frame by scanning, building the frame pixel by pixel, rather than simultaneously acquiring data from each pixel in that singe image frame.

With respect to Claim 34 (similar language exists in Claim 42), the following steps specifically distinguish over Garini's technique:

(d) dispersing the light that is traveling along the collection path into a plurality of light beams, as a function of a plurality of different discriminable characteristics of the light;

(e) focusing each of the plurality of light beams to produce a respective image corresponding to that light beam, thereby simultaneously generating a plurality of images, locations of probes bound to said feature included in the plurality of images being optically discriminated;

With respect to subparagraph (d), Garini's interferometer does separate light collected from the object into the two different optical paths in the interferometer. However, the light is separated by a beam splitter, but the beam splitter simply separates the light into two different beams having the same spectral content. Those beams are then recombined, and the *interference* of those two beams changes the spectral content of the resulting single light beam emitted from the interferometer. The resulting recombined beam is directed onto the detector. Changing the OPD of the interferometer between frames changes the spectral content of each frame. Significantly, Garini's technique does not disperse the light into different light beams *as a function of discriminable characteristics*. The plurality of light beams in Garini's interferometer are identical, and when combined the spectral content of the combined beams is changed, but there is no longer a plurality of beams.

With respect to subparagraph (e), Garini's interferometer discharges a single beam of light that is directed onto a single detector. That detector simultaneously captures all pixels in the frame, but only a single frame is generated at a time. There is simply no teaching or suggestion in Garini that a plurality of images are simultaneously generated by Garini's interferometer. Each new frame is acquired sequentially, after an adjustment to the interferometer has been made.

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The Examiner has correctly noted that in addition to the use of an interferometer, spectral filters and grating can be used to generate images (or frames) having different spectral content. However, once again, such techniques are not based on collecting the different frames simultaneously. With the use of filters, in the prior art, it is known to collect a first image or first frame of a cell using a first filter, and then to change filters to collect a second image or second frame of the cell. The spectral content of the first and second frame (or image) are different, but the different images are not collected *simultaneously*. The same is true of the use of spectral gratings (i.e., slit-type interferometers). There is simply no basis for concluding that any of the spectral grating, spectral filter, or spectral interferometry techniques disclosed by Garini simultaneously generate a plurality of images.

The cited art does not teach or suggest replacing the interferometer disclosed by Garini with an element capable of dispersing the light from the object into a plurality of different light beams as a function of some discriminable characteristic, such that those light beams can be used to simultaneously produce a plurality of different spectral images. It is not apparent that such a modification would solve any problem recognized in the prior art. Thus, independent Claims 34 and 42 patentably distinguish over the cited art. Each claim depending upon Claims 34 and 42 is patentable for at least the same reasons. Accordingly, the rejection of Claims 34-35, 37-40, 42-44, 46, and 49-51 as being anticipated by Garini should be withdrawn.

<u>Rejection of Claims 54 and 55 under 35 U.S.C. § 102</u>

The Examiner has rejected Claims 54 and 55 under 35 U.S.C. § 102 as being anticipated by Garini (U.S. Patent No. 6,066,459). The Examiner asserts that Garini discloses each element of applicants' claimed invention. Applicants respectfully disagree for the following reasons (note Claim 55 has been cancelled, rendering its rejection moot).

Independent Claim 54 is distinguishable over Garini because it encompasses a method for detecting a feature of an object by analyzing an image of the object collected while there is relative movement between the object and the imaging system. Applicants have raised this issue in a prior response. The Examiner maintained the rejection of Claim 54, stating in the current Office Action that "*…it appears that the object and apparatus employed to collect light are inherently required to be in relative motion with each other if simultaneous spectral dispersion imaging of different objects are to be analyzed…*" The logic behind such a conclusion is not apparent. The Examiner specifically

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noted the conclusion was valid *absent evidence to the contrary*. Applicants' prior response did present evidence to the contrary, and the Examiner has not responded to that evidence.

As noted by applicants in a prior response, Garini ***explicitly*** teaches that it is important to keep the relative positions of the sample and the detector fixed so that a pixel on the detector always corresponds to a specific location on the object during scanning. For example, Garini discloses the following (see the first paragraph of column 7): "(i) collecting incident light simultaneously from all pixels of the cell nucleus using collimating optics; (ii) passing the incident collimated light through an interferometer system having a number of elements, so that the light is first split into two coherent beams which travel in different directions inside the interferometer and then the two coherent beams recombine to interfere with each other to form an exiting light beam; (iii) passing the exiting light beam through a focusing optical system which focuses the exiting light beam on a detector having a two-dimensional array of detector elements, *so that at each instant each of the detector elements is the image of one and always the same pixel of the cell nucleus for the entire duration of the measurement, so that the real image of the cell nucleus is stationary on the plane of the detector array and at any time during the measurement the image is still visible and recognizable,* and so that each of the detector elements produces a signal which is a particular linear combination of light intensity emitted by the pixel at different wavelengths, wherein the linear combination is a function of the instantaneous optical path difference…(emphasis added)."

As noted above (first full paragraph of column 17), Garini explicitly teaches that his technique relies on a sequence of images of the same two-dimensional plane (i.e., the sample) at different wavelengths. It appears that Garini's technique requires that relative movement between the object being imaged and the imaging system/detector be prevented. If relative movement between the object and the imaging system/detector is permitted, it appears that Garini's method will not be operative.

With respect to an inherent requirement that there exist relative motion between an object and an imaging system for different spectral images to be simultaneously collected, the Examiner's reasoning is not understood. Applicants' specification describes an imaging system that collects light from an object (such as a cell labeled with different colored probes), separates the collected light into a plurality of different light beams (based on distinguishable characteristics, such as color/wavelength), forms an image from each light beam, and collects each image on a detector, such

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that the images are simultaneously present on the detector. This process can occur regardless of whether there is relative movement between the object and the detector, or the object and detector are not moving relative to each other. Because such an imaging system ***can*** acquire the multiple images necessary for spectral analysis while the object moves relative to the imaging system, the system can acquire data from a very large number of objects very quickly (in the same manner that a flow cytometer can acquire data from a huge number of cells very rapidly). Garini's system can actually acquire more detailed spectral data (the interferometer used by Garini has a greater spectral resolution than the dispersion element in applicants' system, which in the preferred embodiment separates the original light beam into 4-6 different light beams); however, Garini's system cannot collect the spectral data while there is relative movement (noting the relative movement enables data to be collected from many objects in a short period of time, by causing the objects to flow through the imaging system). Thus, applicants' technique has the advantage of collecting less detailed data more rapidly.

In addition to being distinguishable over Garini for the same reasons Claims 34 and 42 distinguish over Garini, Claim 54 further distinguishes over Garini because it indicates that there is relative movement between the object and the imaging system. Accordingly, Claim 54 is patentably distinguishable over the cited art.

<u>Patentability of Newly Added Claims</u>

New Claim 56 is similar to Claim 54 (except the different types of probes that can be used to label a feature with a plurality of optical signaling components have been recited as dependent elements in Claims 57 and 58), and Claim 56 is patentable for substantially the same reasons as Claim 54.

New Claim 59 recites a system configured to implement the method of Claims 34, 42, 54, and 56, specifically including the required dispersing element to achieve the plurality of simultaneously generated images, and a processor configured to perform the analysis required to determine if a labeled feature is present on the object. Claim 59 is patentable for substantially the same reasons as Claims 34 and 42.

New Claim 60 is similar to Claim 42, except that different language has been used to define the different types of probes suitable for labeling the features. Claim 60 has been added to provide alternative language, should the language of Claim 42 be found to be deficient or indefinite.

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New Claim 61 is similar to Claim 54, except that different language has been used to define the different types of probes suitable for labeling the features. Claim 61 has been added to provide alternative language, should the language of Claim 54 be found to be deficient or indefinite.

Relevance of Newly Cited Art

Applicants have concurrently submitted an additional Information Disclosure Statement including references cited in a related foreign application. One such reference (WO 00/55363) discloses labeling cells such that different cell types can be distinguished in a flow cytometer, where the cells are labeled with different ratios of fluorescent labels A and B. Significantly, such a technique is not based on analyzing an image of the cell. Instead, a simple light sensitive detector (not an imaging detector) collects light from each cell, to determine the relative intensity ratio of fluorescent labels A and B. It should be recognized that such a technique is based on analyzing a spectral signal of the cell, not an image of the cell.

The difference between analyzing a spectral signal without an image and a plurality of simultaneously acquired spectral images is significant. Applicants' technology enables a single cell to be labeled with the same color in a plurality of different locations. For example, a first cell that is labeled with blue and red can be distinguished from a second cell labeled with blue and red, by analyzing ***images*** of the cells, to determine the locations of the colored labels.

Consider, for example, a Cell #1, which has been labeled at four different locations. Note each location can be considered to be a different feature. FIGURE 3 of the pending application shows six different images of two different cells (violet, indigo, blue, green, yellow, and red images) that have been simultaneously acquired for each cell (by spectrally dispersing light from each cell before imaging and detecting). Each cell includes four different features labeled by different combinations of blue, green, yellow and red optical signaling components. Referring again to Cell #1 (cell 300 of FIGURE 3), Location 1 (feature 310) is labeled with blue (C1L1=B), Location 2 (feature 308) is labeled with green (C1L2=G), Location 3 (feature 304) is labeled with yellow (C1L3=Y), and Location 4 (feature 306) is labeled with red (C1L4=R). Cell 1 is thus labeled with blue, green, yellow and red, and the ratios of the different colors (blue:green:yellow:red) are: 1:1:1:1.

Next, consider Cell #2 (cell 316 of FIGURE 3), which has also been labeled at four different locations. Location 1 (feature 320) is labeled with blue, green, yellow and red (C2L1=BGYR), Location 2 (feature 322) is labeled with green and red (C2L2=GR), Location 3 (feature 324) is

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labeled with yellow (C2L3=Y), and Location 4 (feature 326) is labeled with blue and red (C2L4=BR). Cell #2 is thus labeled with blue, green, yellow, and red, and the ratios of the different colors (blue:green:yellow:red) are: 4:2:1:2.

Note that because the spectral signal of Cell #1 (1:1:1:1) is different than the spectral signal of Cell #2 (4:2:1:2), the cells can be distinguished based on the spectral signal alone, and imaging is not required. However, consider Cell #3, which has also been labeled at four different locations. Location 1 is labeled with blue (C3L1=B), Location 2 is labeled with blue, green, yellow, and red (C3L2=BGYR), Location 3 is labeled with blue and red (C3L3=BR), and Location 4 is labeled with blue and green (C3L4=BG). Cell 3 is thus labeled with blue, green, yellow, and red, and the ratios of the different colors (blue:green:yellow:red) are: 4:2:1:2. Thus, the prior art approach of analyzing spectral signals, and not spectral images, *cannot* distinguish between Cell #2 and Cell #3. Analyzing a plurality of simultaneously generated spectral images will enable the labeling of the features of Cell #3 to be determined, so that Cell#2 and Cell #3 can be distinguished (noting that if Cell #3 were present in FIGURE 3, the blue, green, yellow and red channels for Cells #2 and #3 would be different). Thus, the claims pending in the present application are clearly distinguishable over the newly cited art.

Accordingly, all of the claims now remaining in the application define patentable subject matter that is neither anticipated nor obvious in view of the prior art cited. The Examiner is thus requested to pass the present application to issue in view of the amendments and the remarks submitted above. If there are any questions that might be addressed by a further telephone interview, the Examiner is invited to telephone the undersigned attorney, at the number listed below.

Respectfully submitted,

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